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# The effect of intracoronary sodium nitrite on the burden of ventricular arrhythmias following primary percutaneous coronary intervention for acute myocardial infarction

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ABSTRACT

*Objective:* Pre-clinical evidence suggests delivery of nitric oxide (NO) through administration of inorganic nitrite suppresses arrhythmias resulting from acute ischaemia and reperfusion (I/R). To date no assessment of whether inorganic nitrite might limit reperfusion arrhythmia has occurred in man, therefore we explored the effects on I/R-induced ventricular arrhythmias in the NITRITE-AMI cohort.

*Methods:* In the NITRITE-AMI cohort, Holter analysis was performed prior to and for 24 h after primary PCI in 80 patients who received either intra-coronary sodium nitrite (N = 40) or placebo (N = 40) during primary PCI for AMI.

*Results:* Ventricular rhythm disturbance was experienced by 100% patients; however, there was no difference in the number between the groups, p = .2196. Non-sustained ventricular tachycardia (NSVT) occurred in 67.5% (27/40) of nitrite-treated patients compared to 89% (35/39) of those treated with placebo (p = .027). There was a significant reduction in both the number of runs (63%, p ≤.0001) and total beats of NSVT (64%, p = .0019) in the nitrite-treated patients compared to placebo. Post-hoc analyses demonstrate a direct correlation of occurrence of NSVT with infarct size, with the correlation stronger in the placebo versus the nitrite group initiating an independent nitrite effect (Nitrite: r = 0.110, p = .499, placebo: r = 0.527, p = .001, p for comparison: 0.004).

*Conclusion:* Overall no difference in ventricular rhythm disturbance was seen with intra-coronary nitrite treatment during primary PCI in STEMI patients, however nitrite treatment was associated with an important reduction in the incidence and severity of NSVT. In view of the sustained reduction of MACE seen, this effect warrants further study in a large-scale trial.



## 1. Introduction

Patients with acute myocardial infarction (AMI) are prone to developing potentially life-threatening ventricular arrhythmias such as ventricular tachycardia (VT) during the acute phase of the AMI. There is evidence that donors of nitric oxide (NO), for example by the administration of organic nitrites/nitrates [1], suppresses arrhythmia as a result of acute ischaemia and reperfusion in both animal models of an AMI [2, 3] but also in patients. In particular, the administration of nitroglycerin in patients was associated with a reduced duration of ventricular ectopic beats over a 48-hour period following AMI [4, 5]. Despite these observations this class of drug, the organic nitrate, is not routinely used to procure benefits in patients suffering AMI due to an overall absence of benefit in clinical trials in ST segment elevation myocardial infarction (STEMI) patients [6–8]. However, there is growing evidence that alternative methods for NO delivery, due to differences in biochemistry, may be more efficacious in AMI, in particular delivery of NO from inorganic nitrate or nitrite [9–11].

Several reports indicate that inorganic nitrite is cardioprotective in pre-clinical models of AMI, reducing reperfusion injury [12, 13]. Importantly, this research has been translated to the clinical setting with 2 separate studies assessing the effect of sodium nitrite on infarct size in patients presenting with ST elevation myocardial infarction (STEMI), namely NIAMI [14] and NITRITE-AMI [15]. Whilst the

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administration of sodium nitrite intravenously prior to primary percutaneous coronary intervention (PCI) had no effect upon infarct size, when administered intra-coronary reductions in infarct size were apparent in patients with occluded arteries at the time of reperfusion (thrombolysis in myocardial infarction [TIMI] category 0–1) [4]. Whether these beneficial effects might also be accompanied by reductions in ventricular rhythm disturbance during primary PCI is yet to be determined. However, support for this possibility comes from preclinical studies where intravenous infusion of sodium nitrite in a canine model of myocardial I/R injury resulted in a profound reduction in the severity and frequency of ventricular arrhythmias. This effect was attributed to delivery of NO specifically within the ischaemic environment possibly due to protein S-nitrosation of key components of mitochondrial respiratory chain and/or S-glutathionylation [16] and thus a localised reduction in oxidative stress.

Thus, the aim of this sub-study was to assess the protective role of inorganic nitrite against acute ischaemia and reperfusion-induced ventricular arrhythmias in STEMI patients undergoing primary PCI in the NITRITE-AMI cohort.

## 2. Methods

### 2.1. NITRITE-AMI study design and participants

NITRITE-AMI was a double-blind, randomised, single-centre, placebo-controlled trial to determine whether the intra-coronary injection of sodium nitrite reduces infarct size in patients with acute STEMI undergoing primary PCI. The trial was approved by an independent ethics committee, the Medicines and Healthcare Products Regulatory Agency, registered in approved registries (NCT01584453, EudraCT nr. 2011-000721-77) and performed in accordance with the Declaration of Helsinki (1996) and the principles of the International Conference on Harmonization–Good Clinical Practice (ICH-GCP) guidelines. Full details of the trial protocol have been published [17]. All appropriate subjects gave written informed consent before being included in the study. After coronary angiography, patients were randomised (1:1) to a high-dose bolus injection of intra-coronary sodium nitrite (1.8 μmol in 10 mL of 0.9% NaCl) or placebo (10 mL of 0.9% NaCl) administered via an over the wire balloon positioned distal to the occlusion in the infarct related artery prior to balloon inflation. All study personnel were blind to treatment allocation until the study and all analyses had been completed.

### 2.2. Ventricular rhythm monitoring

Each patient had a 24-hour Holter Monitor attached immediately after the primary PCI procedure in the cath lab prior to leaving for the coronary care unit (mean time from reperfusion to the placement of the Holter Monitor was 30.1 min). The Holter used was a Spacelabs™ cardiomemo attached with three leads and electrodes. Automated computer analysis of Holter recordings was conducted, with manual over-reading performed by blinded trained cardiac physiologists with analysis focussed upon assessment of ventricular rhythm disturbance. Holter monitor recordings were specifically analysed for ventricular ectopy (isolated ventricular beats), the number of couplets, non-sustained ventricular tachycardia (NSVT) and accelerated idioventricular rhythm throughout the 24-hour period of monitoring. A couplet was defined as 2 consecutive ventricular ectopic beats. NSVT was defined as >3 ventricular ectopic beats at a rate of 120 bpm or more that lasts for <30 s. Accelerated idioventricular rhythm was defined by >3 consecutive ventricular rhythm beats at a rate of <120 bpm. Sustained VT was defined as a VT with a duration of >30 consecutive seconds or leading to haemodynamic compromise within this period. Patient characteristics were recorded through the use of case record forms. Patients in whom 24-hour Holter registration could not be obtained were excluded.

### 2.3. Analysis of heart rate variability

Time and frequency domain indices of heart rate variability were analysed according to the recommendations of Task Force of the European Society of Cardiology (ESC) [18]. Standard deviation of R-R intervals (SDNN), SDNN index (SDNNi) is a measure of variability due to cycles shorter than 5 min, standard deviation of average NN intervals (SDANN), the number of interval differences of successive NN intervals >50 ms (NN50)/total number of NN intervals (pNN50) and square root of the mean squared differences of successive NN intervals (RMSSD) were analysed. Patients with atrial fibrillation, or rhythm disturbances that could interfere with accurate heart rate variability analysis (e.g. frequent ectopic beats, rhythm induced by pacemaker), and patients with inadequate recordings were excluded.

### 2.4. Infarct size

Infarct size was assessed using Creatine kinase (n = 79) and Troponin T (n = 79) Area under the curve (AUC) or Cardiac Magnetic Resonance Imaging (CMR) (n = 68) as previously described [15].

### 2.5. Data and statistical analysis

Analysis was performed using GraphPad™ Prism software version 5.0 for Mac OsX and SPSS version 19, (SPSS Inc., Chicago, Ill). All p values are 2 sided and the border of significance accepted as $p < .05$. Analysis was based on the intention-to-treat principle. Baseline demographic and clinical variables were summarised for each arm of the study. Descriptive summaries of the distributions of continuous baseline variables are presented in terms of percentiles (e.g. median, 25th and 75th percentile), whilst discrete variables are summarised in terms of frequencies and percentages. Comparisons are between the sodium nitrite-treated and placebo control-treated group. Statistical analyses were conducted blind to the treatment groups. For comparisons between normally distributed data statistical comparisons were performed using unpaired *t*-tests and non-normally distributed data with non-parametric testing (Mann–Whitney). Determination of correlations was performed using the Pearson's correlation coefficient analysis of least-squares and expressed as 95% confidence intervals.

## 3. Results

Eighty patients were recruited into NITRITE-AMI (40 in the control group and 40 in the nitrite group). All 80 patients underwent 24-hour Holter monitoring; however, one had an incomplete dataset and was excluded leaving a total of 79 patients with analysable data. As previously reported in the main NITRITE-AMI study, cohort baseline characteristics are shown in table S1, and were similar between the treatment groups. Aside from the study IMP, no differences in treatment (medication), timing of medication initiation or devices were seen between the 2 groups either pre, post PCI and out to 12 months (Table 1). The mean age of the trial participants was 57 years, with 84% male. 25% of the cohort had anterior infarcts with similar numbers in both treatment groups. Stenting of the culprit lesion was performed in 97.5% of all patients. For full details see Jones et al. [4].

### 3.1. Incidence of arrhythmias

Overall ventricular rhythm disturbance was experienced by all 79 (100%) patients. All patients experienced isolated ventricular ectopics (median 433, IQR 137–1061), 94% of patients experienced ventricular couplets (median 12, IQR 4–35), 77% of patients experienced accelerated idioventricular rhythm (median 11 beats, IQR 3–42) and 78% of patients experienced NSVT (median 20 beats, IQR 3–60). Over the 24-hour period of measurement 46.8% of the arrhythmias occurred in the 1st 8 h, with 33% between 8–16 h and the remaining 20.2% between 16 and 24 h. Both NSVT and AIDR were seen throughout the 24-hour period; however, in the first 8 h, 63.2% of the arrhythmias seen were AIDR, and in the last 8 h, 82.1% of the arrhythmias were NSVT indicating a preponderance of AIDR earlier in the time period.

No patients had episodes of either sustained VT or ventricular fibrillation (VF) post IMP delivery, although 2 patients required defibrillation for pulseless VT/VF prior to the primary PCI. These 2 patients were successfully treated with primary PCI post defibrillation (both with 1× shock), both with drug-eluting stents to the circumflex. Both had uncomplicated in-patient courses being discharged without complication.

Overall there was no difference in the incidence of total ventricular ectopic burden between the 2 treatment groups either as a total number of VEs (Nitrite median VEs 398 (IQR 104–1253) vs placebo 497 (297–1007), $p = .2196$) or as a percentage of total ventricular activity (Nitrite 0.35% (0.09–1.25) vs placebo 0.46 (0.25–0.93), $P = .1917$) (Fig. 1). Additionally, no difference was seen in the incidence of couplets between the 2 treatment groups ($p = .81$). The incidence of VEs was positively correlated with myocardial infarct size as assessed by both cardiac enzymes ($r = 0.277$, $p = .014$) and CMR ($r = 0.316$, $p = .012$) (Fig. S1).

### 3.2. NSVT was reduced by nitrite treatment

NSVT occurred in 67.5% (27/40) of nitrite-treated patients compared to 89% (35/39) of those treated with placebo ($p = .027$). In addition, both the number of runs (63%, $p \leq .0001$) and total beats of NSVT (64%,